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May 26, 2004

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APPLICATION NUMBER: ***60/506,716***
FILING DATE: ***September 30, 2003***
RELATED PCT APPLICATION NUMBER: *PCT/US04/10191*

CD DISK IS THE APPLICATION FOR THE ABOVE REFERENCED INFORMATION

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Due to the format in which this priority document and accompanying certification was transmitted, the International Bureau has been unable to upload these documents in full into its information systems. Only a copy of the certification page and the first four pages of the specification are enclosed herewith. The International Bureau will provide a complete copy of this document upon request.

DIAGNOSIS OF HYPERINSULINEMIA AND TYPE II DIABETES AND PROTECTION AGAINST SAME (II.1)

Cross-Reference to Related Applications

The instant application adds 6 month expression data to the disclosure of US Prov. Appl. 60/460,415, filed April 7, 2003 (KOPCHICK6-USA).

In U.S. Provisional Appl. Ser. No. 60/458,398 (our docket Kelder1-USA), filed March 31, 2003, we describe the identification of genes differentially expressed in normal vs. hyperinsulinemic, hyperinsulinemic vs. type II diabetic, or normal vs. type II diabetic mouse liver. Forward- and reverse-substracted cDNA libraries were prepared, clones were isolated, and differentially expressed cDNA inserts were sequenced and compared with sequences in publicly available sequence databases. The corresponding mouse and human genes and proteins were identified. Favorable genes/proteins so identified included (1) NP_000767: cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 3; (2) AAG31034: SYT/SSX4 fusion protein ; and (3) NP_003158: sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1; sulfotransferase family 2A, dehydroepiandrosterone (DHEA)-preferring, member 1. Unfavorable proteins included (4) NP_004884: H2A histone family, member Y isoform 2; histone macroH2A1.2; histone macroH2A1.1; (5) AAH37738: Unknown (protein for MGC:33851); (6) NP_068839: integral membrane protein 2B ; (7) CAA28659: S-protein ; and (8) AAA51560: alpha-1-antichymotrypsin precursor. Mixed proteins included (9) NP_000769: cytochrome P450, subfamily IVA, polypeptide 11; fatty acid omega-hydroxylase; P450HL-omega; alkane-1 monooxygenase; lauric acid omega-hydroxylase; (10) NP_006206:serine (or cysteine) proteinase inhibitor, clade A ; (11) NP_004489: one cut domain, family member 1; hepatocyte nuclear factor 6, alpha; and (12) NP_775491: liver-specific uridine phosphorylase. Gene chip technology was not used. Two of the genes (NM_007818 and NM_007822) were also identified in the present case.

The use of differential hybridization to identify genes and proteins is also described in our Ser. No. PCT/US00/12145 (Kopchick 3A-PCT), Ser. No. PCT/US00/12366 (Kopchick4A-PCT), and Ser. No. 60/400,052 (Kopchick5). All of the above applications are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to various nucleic acid molecules and proteins, and their use in (1) diagnosing hyperinsulinemia and type II diabetes, or conditions associated with their development, and (2) protecting mammals (including humans) against them.

Description of the Background Art

Diabetes

Diabetes mellitus is a pleiotropic disease of great complexity. The two major types have been termed type I or insulin-dependent diabetes mellitus (IDDM) and type II or non-insulin-dependent diabetes mellitus (NIDDM). Type II diabetes is the predominant form found in the Western world; fewer than 8% of diabetic Americans have the type I disease.

Type I diabetics are often characterized by their low or absent levels of circulating endogenous insulin, i.e., hypoinsulinemia (1). Islet cell antibodies causing damage to the pancreas are frequently present at diagnosis. Injection of exogenous insulin is required to prevent ketosis and sustain life.

Early Type II diabetics are often characterized by hyperinsulinemia and resistance to insulin. Late Type II diabetics may be normoinsulinemic or hypoinsulinemic. Type II diabetics are usually not insulin dependent or prone to ketosis under normal circumstances.

Type II Diabetes

Type II diabetes (formerly known as non-insulin dependent diabetes, NIDDM) is the most common form of elevated blood glucose (hyperglycemia). Type II diabetes is a metabolic disorder that affects approximately 17 million Americans. It is estimated that another 10 million individuals are "prone" to becoming diabetic. These vulnerable individuals can become resistant to insulin, a pancreatic hormone that signals glucose (blood sugar) uptake by fat and muscle. In order to maintain normal glucose

levels, the islet cells of the pancreas produce more insulin, resulting in a condition called hyperinsulinemia. When the pancreas can no longer produce enough insulin to compensate for the insulin resistance, and thereby maintain normal glucose levels, Type II diabetes (hyperglycemia) results.

Complications of diabetes (end organ damage) include retinopathy, neuropathy, and nephropathy (traditionally designated as microvascular complications) as well as atherosclerosis (a macrovascular complication).

Early stages of hyperglycemia can usually be controlled by an alteration in diet and increasing the amount of exercise, but drug treatment, including insulin, may be required. It has been shown that meticulous blood glucose control can often slow down or halt the progression of diabetic complications if caught early enough (1). However, tight metabolic control is extremely difficult to achieve.

Little is known about the disease progression from the normoinsulinemic state to the hyperinsulinemic state, and from the hyperinsulinemic state to the Type II diabetic state.

As stated above, type II diabetes is a metabolic disorder that is characterized by insulin resistance and impaired glucose-stimulated insulin secretion (2,3,4). However, Type II diabetes and atherosclerotic disease are viewed as consequences of having the insulin resistance syndrome (IRS) for many years (5). The current theory of the pathogenesis of Type II diabetes is often referred to as the "insulin resistance/islet cell exhaustion" theory. According to this theory, a condition causing insulin resistance compels the pancreatic islet cells to hypersecrete insulin in order to maintain glucose homeostasis. However, after many years of hypersecretion, the islet cells eventually fail and the symptoms of clinical diabetes are manifested. Therefore, this theory implies that, at some point, peripheral hyperinsulinemia will be an antecedent of Type II diabetes. Peripheral hyperinsulinemia

can be viewed as the difference between what is produced by the β cell minus that which is taken up by the liver. Therefore, peripheral hyperinsulinemia can be caused by increased β cell production, decreased hepatic uptake or some combination of both. It is also important to note that it is not possible to determine the origin of insulin resistance once it is established since the onset of peripheral hyperinsulinemia leads to a condition of global insulin resistance.

Multiple environmental and genetic factors are involved in the development of insulin resistance, hyperinsulinemia and type II diabetes. An important risk factor for the development of insulin resistance, hyperinsulinemia and type II diabetes is obesity, particularly visceral obesity (6,7,8). Type II diabetes exists world-wide, but in developed societies, the prevalence has risen as the average age of the population increases and the average individual becomes more obese.

Obesity is a serious and growing problem in the United States. Obesity-related health risks include high blood pressure, hardening of the arteries, cardiovascular disease, and Type II diabetes (also known as non-insulin-dependent diabetes mellitus, Type II diabetes) (9,10,11). Recent studies show that 85% of the individuals with Type II diabetes are obese (12).

Growth Hormone

Growth hormone has many roles, ranging from regulation of protein, fat and carbohydrate metabolism to growth promotion. GH is produced in the somatrophic cells of the anterior pituitary and exerts its effects either through the GH-induced action of IGF-I, in the case of growth promotion, or by direct interaction with the GHR on target cells including liver, muscle, adipose, and kidney cells. Hyposecretion of GH during development leads to dwarfism, and hypersecretion before puberty leads to gigantism. In adults, hypersecretion of GH results in acromegaly, a